Noninvasive Detection of Motor-Evoked Potentials in Response to Brain Stimulation Below the Noise Floor—How Weak Can a Stimulus Be and Still Stimulate

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***Abstract*—Motor-evoked potentials (MEP) are one of the most important responses to brain stimulation, such as supra-threshold transcranial magnetic stimulation (TMS) and electrical stimulation. The understanding of the neurophysiology and the determination of the lowest stimulation strength that evokes responses requires the detection of even smallest responses, e.g., from single motor units, but available detection and quantization methods are rather simple and suffer from a large noise floor. The paper introduces a more sophisticated matched-filter detection method that increases the detection sensitivity and shows that activation occurs well below the conventional detection level. In consequence, also conventional threshold definitions, e.g., as 50 μV median response amplitude, turn out to be substantially higher than the point at which first detectable responses occur.**

The presented method uses a matched-filter approach for improved sensitivity and generates the filter through iterative learning from the presented data. In contrast to conventional peak-to-peak measures, the presented method has a higher signal-to-noise ratio (≥14 dB). For responses that are reliably detected by conventional detection, the new approach is fully compatible and provides the same results but extends the dynamic range below the conventional noise floor. The underlying method is applicable to a wide range of well-timed biosignals and evoked potentials, such as in electroencephalography.

I. Introduction

Motor-evoked potentials (MEP) are an important response phenomenon in brain stimulation. If motoneurons in the primary motor cortex are activated directly or indirectly, they respond with action potentials, which are transmitted down the spinal cord to the lower motoneurons [1, 2]. The lower motoneurons route the signals to the muscles, where they can be detected as MEP waves through electromyography (EMG). MEPs provide one of the few directly observable responses of the brain to stimuli and individualize the stimulation strength. Furthermore, MEPs are a key to understanding the biophysical and neurophysiological mechanisms of brain stimulation, to establishing safety limits, and to achieving individual dosing [3, 4]. In FDA-approved treatment with transcranial magnetic stimulation (TMS), for instance, the so-called motor threshold is defined based on MEPs and is the key safety as well as dosage parameter [5].

The response amplitudes of several MEPs graphed over the corresponding stimulation strengths forms an s-shaped curve, often named as input–output (IO) or recruitment curve [6, 7]. For high stimulation strengths, the responses saturate and form the high-side plateau of the sigmoidal IO curve around several millivolts, dependent on the specific muscle. If the stimulation strength is reduced, the response amplitude decreases monotonically until the responses appear to cease entirely and fall below a low-side plateau that is formed by endogenous activity, biosignals from unrelated neural and muscular sources, and recording noise. Thus, the dynamic range of MEP amplitudes can exceed a factor of 1000 [8].

Typically, the noise floor forming the low-side plateau for a resting motor system of a conscious subject, e.g., for TMS, can reach 10 μV [8]. The motor threshold is defined slightly above this plateau at 50 μV median response amplitude as a compromise between detecting also subtle responses and sufficient detection robustness [4]. Such threshold definition assume that they are close to the smallest occurring evoked activity. The noise floor, however, is not a purely technical property of the used amplifier, but for modern amplifiers widely depends on external conditions, such as the electrode and source impedance, body temperature, and biosignals from unrelated sources. Thus, simple technical advances of amplifiers do not solve the problem. According to the established interpretation, smaller responses causally evoked by stimulation of motor efferences might either not exist or could not be detected for physical reasons.

So-called active stimulation into a pre-activated motor system is used to find smaller effects of single TMS pulses [9]. However, it is not obviously clear if such active pulses actually immediately depolarize neurons or only modulate endogenous signals. First approaches for looking below the noise floor to find MEPs averaged the responses to many individual stimuli, as a solution that is also typical for other subtle biosignals, such as in electroencephalography (EEG) [10]. Although these experiments hinted that there is evoked motor activity well below the motor threshold, averaging does not solve the problem. Averaging of responses to several different stimulation strengths or even of an entire IO curve would re-

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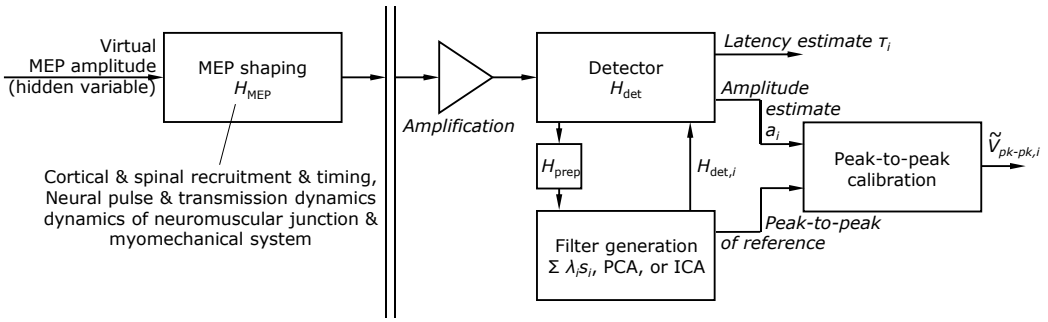

Figure 1. Assumed equivalent model of the MEP generation and block diagram of the presented detection method.

quire many trials and lead to unacceptably long session durations. More importantly, however, MEPs are inherently highly variable, which reflects endogenous signaling at the site of activation and is part of the information [8, 11]. Averaging extinguishes this variability and the contained information. Furthermore, the variability is not Gaussian distributed but has a highly skewed distribution so that averaging does not result in an exemplary representation of the many noisy individual MEPs, but is dominated by outliers [12].

In this paper, we introduce an MEP analysis method based on a learning matched-filter detection, which can quantify the output amplitude more accurately and use the entire spectral signal bandwidth. The method estimates a detection filter concurrently through iterative learning from previous responses. The approach achieves a high signal-to-noise ratio (SNR) through extraction of the similarities of many responses and therefore shares some characteristics with averaging but translates them to the individual MEPs. In contrast to simple time-synchronized averaging approaches, the matched-filter method does not require repetitions at the same stimulation strength but merges information from all applied valid stimuli with a wide range of stimulation strengths. In consequence, it offers better signal-to-noise ratios at notably lower numbers of stimuli and undistorted amplitude readings for each MEP.

II. Methodology for the Detection of MEPs within the Noise Floor

MEPs appear in response to a stimulus in the primary motor cortex as a typically bipolar wave with a bandwidth of less than 200 Hz. Electrophysiologists conventionally quantify the amplitude of MEPs by their peak-to-peak voltage [13]. Although this established method is simple, it is relatively insensitive to weak MEP waves but highly susceptible to noise. As it uses positive and negative maxima, it converts even simple interference and noise, such as additive Gaussian noise, into highly skewed and mathematically intricate extreme-value distributions [8]. Strictly, those extreme-value distributions would have to be taken into account for correct statistical analysis, but practically never are.

Some authors suggested the use of the area under the MEP curve instead of MEP peak-to-peak voltage for higher accuracy [14-16]. However, despite the noise-reducing low-pass-filtering properties, the MEP area has several severe disadvantages. It depends on the amplifier filter properties, such as the high-pass filter cutoff; it requires a definition of start and end of an MEP, which influences the readings; it provides impractical units (volt-seconds) and is incompatible with traditional peak-to-peak quantification as well as established safety rules [4]. In consequence, MEP area is rarely used.

In contrast to conventional approaches, the proposed detection method exploits the entire spectral bandwidths of MEPs. We assume that the MEP amplitude is an actual or virtual value that underwent shaping through the neuromuscular transmission system as shown in Fig. 1. Without loss of generality, nonlinear transformations are not required. Ideally, the detector maximizes the signal while minimizing the impact of noise. The in principle most appropriate linear detector in the presence of additive Gaussian noise, such as the dominant share of amplifier and electrode noise, is a correlation detector or a filter with the complex conjugated and mirrored spectrum, i.e., time-reversed impulse response of the assumed MEP shaping filter (see Fig. 1) [17]. As the method is entirely linear, it can be linearly linked and calibrated to conventional peak-to-peak readings. However, whereas for usual detectors, the matching sender and receiver filter are systematically designed, the MEP shaping filter here is merely conceptual and practically a hidden property. Thus, the ideal detection filter has to be estimated as well. The following will describe the three modules of the method, specifically, the detection, filter estimation, and calibration modules.

Detection. The detection process assumes that the optimum filter h_{det} is known and provided by a filter estimation module. The detector receives the digitized EMG signals s_i ideally unfiltered except for anti-alias filtering and dc baseline removal. We implemented the detection filter as a digital filter since the filter tabs can be dynamically updated. The amplitude reading of the MEP a_i is the peak of the filter output. The temporal position of the peak provides the latency of the MEP. If the latency is not relevant and relatively independent from the amplitude, the MEP amplitude reading can be sampled at a fixed position instead of peak detection. The wide bandwidth of detection filter achieves the maximum noise suppression level that linear filtering can achieve and does not skew the noise distribution:

$$a_i = \int_{\mathbb{R}^+} h_{\mathrm{det}}(\tau) s_i(t-\tau)\,\mathrm{d}\tau \Big|_{\text{sampling time}} \tag{1}$$

Filter estimation. We generate the detection filter by stimulus-triggered sampling of each MEP. We automatically suppress

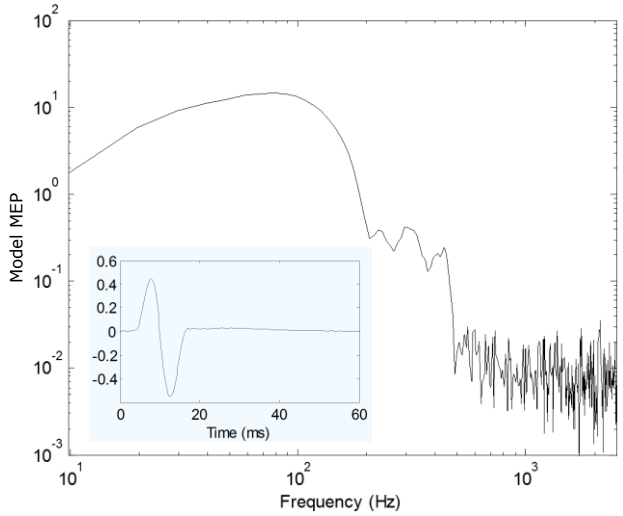

Figure 2. Spectrum and time course (inset) of the iteratively learnt reference MEP, which the detection module uses for estimating the MEP amplitude.

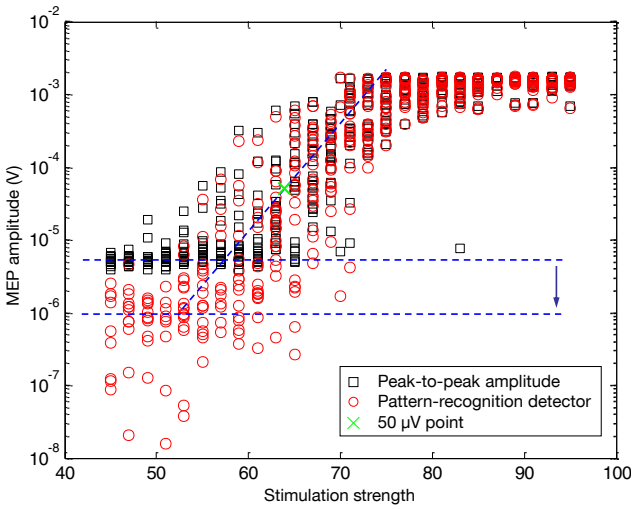

Figure 3. IO curves extracted via conventional (black squares) and the more sensitive detection method proposed here (red circles). Whereas responses with high response amplitudes and therefore high SNR coincide in both methods, fainter responses tend to be overestimated in the conventional peak-to-peak metric due to noise and noise misinterpreted as signals forms a low-side plateau at small stimulation strength.

the initial 5 ms of the MEP recording to eliminate any stimulus artifacts, which would correlate well within all samples. Dependent on various factors and stimulation targets, the onset of MEPs is larger than 15 ms [18, 19]. The time-synchronized recordings are high-pass filtered by h_{prep}, time-inverted, and stored in a matrix. After each pulse, the average of that ensemble is normalized and forms the newest detection filter. In addition, the filter estimation module forms a reference model MEP $M(t)$ as the average of all MEPs (see Fig. 2). The SNR of both the filter and the model MEP on average grows with $\sqrt{n}$ for n MEP curves $s_i(t)$ and uncorrelated additive Gaussian noise. Thus, in each iteration i, the detection filter $h_{\text{det}}(t) = M(-t)$ is updated through a (optionally weighted) sum by

$$h_{\text{det},i} = \sum_{i \le n} \lambda_i s_i^*(-t). \tag{2}$$

In the following, the weight factors are used to normalize the MEPs to a similar amplitude so that $\lambda_i = 1/a_i$. As the filter successively improves in the process, the amplitude estimates do as well. An iterative process according to $\lambda_i^j = (1/a_i)^{j-1}$ to improve the filter recursively with the entire MEP dataset with only a few iterations j converges well without the need for numerical relaxation. The iteration runs online during data acquisition and updates the entire dataset after each new MEP.

Calibration to peak-to-peak detection. Above MEP amplitude reading only provides relative values as it outputs how much a new recording matches the reference MEP. However, as it is proportional to the amplitude, it can be calibrated to be compatible with conventional peak-to-peak measurements with the reference MEP. As the SNR of the model MEP is by approximately $\sqrt{n}$ higher than of an individual MEP, its peak-to-peak reading far less depends on noise. The individual MEP can inherit its peak-to-peak reading and thus also the lower noise from the model MEP through the product of the model MEP's peak-to-peak rating weighted by the estimated similarity $a_i(t)$ of the individual MEP and the model MEP, which is given by the filtered individual MEP by

$$\tilde{V}_{\text{pp}} = \left(\max_{\text{t}}(M) - \min_{\text{t}}(M)\right) \cdot a_i. \tag{3}$$

III. Experimental Evaluation

We evaluated the method experimentally as approved by the Duke University Institutional Review Board. The subject of the study underwent single-pulse TMS (MagVenture MagPro X100) over the representation of the first dorsal interosseous muscle in the left primary motor cortex. The individual pulses were at least 8 s apart and their timing was randomized to not follow the subject's expectation. A focal figure-of-eight coil (MagVenture B65) was positioned approximately 45° to the longitudinal fissure. MEPs were recorded and sampled through surface Ag/AgCl electrodes and an EMG amplifier (Biometrics K800 SX230FW) at 5 kHz and 16 bit. MEPs with activity of more than 40 µV within a window of 200 ms before the TMS pulse were excluded from the analysis. The entire dataset contained more than 500 individual MEPs of a wide range of stimulation strengths.

Figure 3 shows two IO curves extracted from the data with conventional peak-to-peak MEP amplitude estimation (black squares) and the proposed method (red circles) from the same recording. For large MEPs, both concur as expected. For smaller MEPs, where the SNR drops, the peak-to-peak detection tends to pick up noise and overestimate the actual MEP. At the lower end of the stimulation strength, peak-to-peak detection entirely fails to detect any responses and forms a low-side plateau at a few microvolts, representing the noise cut-off.

In the proposed method, in contrast, the data points reach below the conventional peak-to-peak detection limit and, importantly, the trend continues monotonically with the same slope as in the upper section. Thus, the MEPs below the conventional peak-to-peak detection limit are not noise but show the expected stimulation-strength dependency. The presented

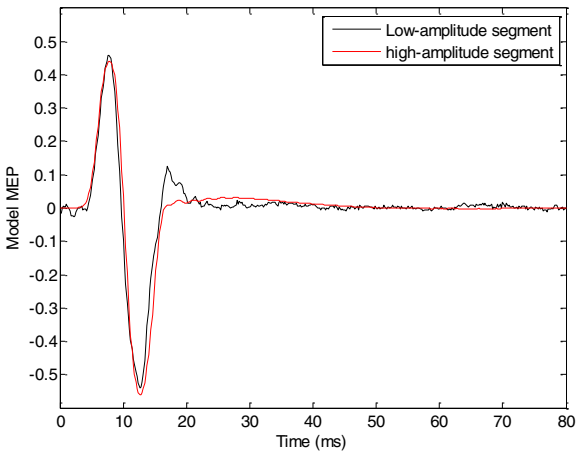

Figure 4. Reference MEPs generated from two amplitude segments, particularly those MEPs above 100 µV and those below, correlate at 0.970.

method reduces the low-side plateau and thus the detection limit by a factor of more than 5 (14 dB).

The 50 µV point, once selected as reference level for the motor threshold, is no longer at the onset of first detectable MEPs, but is almost in the center of the sigmoid (see Figure 3). Thus, it turns out that the point that once was considered a threshold stimulation strength at a level were first responses occur is rather in the middle of the dynamic range of MEPs.

The filter estimation method extracts the similarities of all responses in a learning paradigm to form the filter for the detector. As this approach takes all valid responses into account, it assumes that the MEPs do not change substantially, particularly not with amplitude. We set up a detector that trained two filters, a low-amplitude filter trained from and applied to only MEPs with less than 100 µV and a high-amplitude filter for the others, which entails almost equally sized MEP groups. Figure 4 depicts the extracted reference MEPs. The here important correlation coefficient of the two amounts to 0.970 and the low-amplitude cohort appears to show more high-frequency content originating from noise and potential granularity effects associated with the few involved individual motor unit activity. Similarly, the reference MEP was stable over time (not plotted for space reasons). We grouped the MEPs of the 75 minutes of the TMS session in ten intervals. The pairwise correlation between the individual MEP references was between 0.984 and 0.996. Thus, the error of the amplitude estimation of an individual MEP in the presented detector, which is based on correlation after all, does not exceed 3%, while the group error per definition of the filter learning method approaches zero. Considering the exponential nature of the IO curve, errors on that level appear small.

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